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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Campbell Rogers, Elazer R. Edelman, and Daniel I. Simon

Serial No.: 09/776,533 Group Art Unit: 1644

Filed: February 7, 2001 Examiner: Phillip Gambel

For: *MODULATION OF VASCULAR HEALING BY INHIBITION OF LEUKOCYTE ADHESION AND FUNCTION*

Box DAC
Assistant Commissioner for Patents
Washington, D.C. 20231

PETITION FOR SUPERVISORY REVIEW BY THE COMMISSIONER

Sir:

Pursuant to 37 C.F.R. § 1.144, applicants petition the Commissioner to review the restriction requirement set forth in the Office Action mailed June 11, 2002, and made final in the Office Action mailed September 6, 2002. Applicants enclose the required fee of $130.00 along with this petition. Should an additional fee be required, the Commissioner is hereby authorized to charge any such fee to Deposit Account No. 50-1868.

Remarks

The Office Action mailed June 11, 2002, divided the claims into 24 groups. These are appended for the convenience of the Commissioner in Appendix A. This

application is a continuing application of 08/823,999 filed March 5, 1997, to which this application claims priority. In prosecution of the parent application, a restriction requirement was imposed by the *same examiner* (See Appendix B), where the *same claims* were divided into only two groups, and an election of species was made. This application was not only prosecuted on this basis but is currently on appeal at this time, with data and arguments submitted during prosecution and on appeal that were based on the original restriction requirement. These arguments are prejudicial to any prosecution by applicants that would have to be made in the present application based on the current restriction requirement.

It is respectfully requested that the Commissioner review the imposed restriction requirement and make the same restriction requirement as the parent, based on the same claims as now pending in this case.

CLAIMS 1-12 ARE PENDING

In the response filed July 11, 2002, applicants elected for prosecution of claims 1-12, based on the elected species of Mac-1-specific antibodies. Claims 13-17 were cancelled. The claims as pending are attached as an Appendix for the convenience of the Commissioner (Appendix A).

THE CURRENT RESTRICTION IS IMPROPER

Applicants believe that the restriction requirement imposed in the present application to Groups I to XII is improper. First, contrary to the Examiner's assertion,

Group I- XII claims are related to each other. Claims 1-12 are directed to the methods for the inhibition of stenosis or restenosis using the various species in the Groups I to XII claims which fall within the single method of claim 1. In addition, all of the claims 2-12 depend from claim 1, requiring administering a compound which specifically inhibits or reduces integrin-mediated leukocyte adhesion or function. Group I to XII claims are not so materially different from each other so as to require restrictions into separate groups of claims (see MPEP 806.05(f)).

Further, "where the claims of an application define the same essential characteristics of a *single* disclosed embodiment of an invention, restriction therbetween should never be required. This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition." (MPEP 806.03)

Claims 1-12 all clearly define essential characteristics of the single embodiment of the invention that being *a method of inhibiting or reducing stenosis or restenosis of a blood vessel.* The examiner has not only divided the generic claims into different groups based on description in the specification of what molecules can be used, but further divided by what the molecules bind to, *even in the complete absence of any such limitations in the claims!*

The restriction made in the parent application was a proper restriction requirement as defined in MPEP 806.05(e) which describes the restriction of claims as

process and apparatus for its practice. The examiner stated "the product as claimed can be used in a materially different process such as affinity purification or detection assays". "Process and apparatus for its practice can be shown to be distinct inventions, if either or both of the following can be shown: (A) that the process as claimed can be practiced by another materially different apparatus or by hand; or (B) that the apparatus as claimed can be used to practice another and materially different process." In this instance the applicants elected the process and cancelled claims directed to the apparatus for its practice.

THE CURRENT CLAIMS DEFINE PROPER SPECIES

The examiner states in the office action mailed September 6, 2002 that the restriction was set forth because these are not proper species. The Examiner is wrong and explicitly contradicted by the statements made in the parent application with respect to the exact same claims when he made an election of species requirement. These are proper species. The Patent and Trademark Office defines "species" as specifically different disclosed embodiments of an invention. (Chisum 4:12.03[3][a]). Another definition states that the two species must have different structures and modes of action. The integrins and their ligands were accepted as proper distinct species in the parent application. Applicants respectfully submit that a search of the prior art relating to one of these species does not impose a serious burden on the examiner, *and that, moreover, the examiner has already conducted the search in the parent application now on*

Does not appear to be true

appeal!

Further, the MPEP states that species, "while usually independent, may be related under the particular disclosure. Where inventions as disclosed and claimed are both (A) species under a claimed genus and (B) related, then the question of restriction must be determined by both the practice applicable to election of species and the practice applicable to other types of restrictions such as those covered in MPEP 806.05-806.05(i)." (MPEP 806.04(b))

The relationship between species is disclosed. Compounds that inhibit leukocyte adherence by inhibiting integrins or integrin ligands as stated on page 7 line 26 to page 8 line 6. The claimed method is directed to *a method of inhibiting stenosis or restenosis by inhibiting integrin-mediated cell adhesion.* Clearly blocking different members of the integrin family or an integrin ligand is encompassed by the scope of this method. "Current Patent and Trademark Office policy precludes restriction, even in the case of multiple species, unless the two groups of claims are patentable over each other (*i.e.*, neither is obvious in the light of the other) (Chisum 4:12.03).

The similarity of the members of the 24 groups is further demonstrated by the fact that they only belong to two class/subclass combinations. In the restriction requirement of the parent application, the examiner stated that the integrins and their receptors constituted distinct species because their structures and modes of action are different. Mac-1, LFA-1, p150,95, and CD11d/CD18 are all integrins. The ligands for

these integrins overlap.

The MPEP states that to be patentably distinct, two subjects as disclosed are related, but are capable of separate manufacture, use, or sale as claimed, and are patentable (novel and unobvious) over each other (MPEP 802.01). However, in the parent application prior art against the elected species was used as a basis to rejection the claims to the non-elected species and this rejection is on appeal. Is the examiner now saying this rejection was wrong?

Not true

These species are clearly related and do not constitute 24 separate patentably distinct inventions. The integrins and their ligands are grouped together and related as described in the disclosure. The integrins are disclosed together on page 7, line 16-21 of the specification, the ligands for the integrins are disclosed together on page 7, 21-25 and once again on page 9, lines 4-10. The compounds to inhibit integrin-mediated adhesion are disclosed together on page 7 line 26 to page 8, line 6. An election of species is proper in this instance.

THE GENERIC CLAIMS ARE PROPER

The MPEP defines a generic claim as including "no material element additional to those recited in the species claims, and must comprehend within its confines the organization covered in each of the species." (MPEP 806.04(d))

The present claims are all directed to *a method of inhibiting or reducing stenosis or restenosis by inhibiting integrin-mediated cell adhesion.* Proper use of

generic and species claims is used as defined by 37 CFR § 1.141. **Claims 1-4 and 11-12 are generic.** There is **no limitation** in these claims specific to integrins, integrin ligands or specific compounds to inhibit them. Clearly, **the examiner is trying to impose limitations NOT PRESENT IN THE CLAIMS through the vehicle of a restriction requirement.** These claims are included below for illustration.

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systematically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and

liposomes.

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

In the restriction requirement of the parent application, the examiner stated that claim 1 and claim 13 (now cancelled) are proper generic claims. It is inconsistent for a generic claim previously satisfying the requirements of MPEP 806.04(d) to be deemed not generic at a later date.

THESE SAME CLAIMS HAVE ALREADY BEEN PROSECUTED TOGETHER

The parent case based on the claims as originally restricted, has been examined, evidence submitted, and is now on appeal. It would unfairly prejudice the Applicants to make a restriction requirement of the same claims which have already been prosecuted and which are now waiting at the Board of Appeals. Arguments have been made arguing results with one species are predictive of results with another species, all of which are joined by a common function (i.e. the inhibition of leukocyte adhesion and function). It is well established that a genus can be linked by a common function, to achieve a common result: in this case, modulation of vascular healing, and in particular, prevention or mitigation of restenosis.

The examiner has cited MPEP 811.04 to justify the restriction requirement

imposed differently from the parent application. "Even though inventions are grouped together in a requirement in a parent application, restriction or election among the inventions may be required in the divisional application, if proper." The present application is a continuation of application 08/823,999, not a divisional. Further, the MPEP states a restriction may be required "if proper". The current restriction is clearly not proper as division of the claims is incorrect, making further restriction under this section of the MPEP improper. It is by the same examiners own logic that the initial restriction in the parent was imposed.

In *Mark I Marketing Corp. v. R.R. Donnelley & Sons Co.* (1995), 154. the Federal Circuit stressed that `` 'The prosecution history must be examined as a whole in determining whether estoppel applies.' '': ``Thus, the relevant prosecution history here includes not only the ... application [upon which the patent issued] but also the parent ... and grandparent ... applications. Chisum 5A:18.05[2][d][ii]

The Examiner should be bound by the final decisions he rendered during the prosecution of claims 1-12 as a single invention in the parent application. These claims have been prosecuted together as a group under the same prior art references in office actions of the parent. The previous history of prosecuting this group of claims as one invention acknowledges that they are related. It is inconsistent to restrict the exact same claims differently in this application than in the parent application.

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SUMMARY

The current restriction imposed on the claims of the present invention is improper. This restriction is inconsistent with the guidelines for restriction practice delineated by the MPEP. The claims of this invention are directed to the method for inhibiting stenosis or restenosis and the compositions directed to this method. The restriction requirement set forth in the parent application most appropriately divides the claims as directed by the MPEP. In the present case, the Examiner is using the vehicle of restriction requirement to impose limitations not present in the claims. Applicants respectfully request that the same restriction be imposed as in the parent, dividing the claims into two groups (i.e. Claims 1-12 and 13-17) with an election of species, for prosecution.

Favorable consideration of this petition is earnestly solicited.

Respectfully submitted,

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APPENDIX A: *Clean Copy of Claims as Pending*

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and liposomes.

5. The method of claim 1 wherein the integrin is selected from the group consisting of Mac-1, LFA-1, p150,95, and CD11d/CD18.

6. The method of claim 5 wherein the integrin is Mac-1.

7. The method of claim 6 wherein the ligand is selected from the group consisting of ICAM-1, fibrin(ogen), C3bi, and factor X.

8. The method of claim 1 wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells; molecules which inhibit expression of the integrins or their ligands, and

peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells or tissues.

9. The method of claim 5 wherein the integrin is LFA-1 and the ligand is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3.

10. The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1.

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

APPENDIX B: *Restriction Requirement imposed June 11, 2002*

Group I, claims 1-8, 10-12, drawn to methods of inhibiting stenosis or restenosis with Mac-1-specific antibodies (Class 424 , subclass 130.1)

Group II, claims 1-5, 8-9, 11-12, drawn to methods of inhibiting stenosis or restenosis with LFA-1-specific antibodies (Class 424, subclass 130.1)

Group III, claims 1-5, 8, 11-12, drawn to methods of inhibiting stenosis or restenosis with p150,95-specific antibodies (Class 424 , subclass 130.1)

Group IV, claims 1-5, 8, 11-12, drawn to methods of inhibiting stenosis or restenosis with CD11d/CD18-specific antibodies (Class 424 , subclass 130.1)

Group V, claims 1-4, 7-9, 11-12, drawn to methods of inhibiting stenosis or restenosis with ICAM-1 (Class 514, subclass 8)

Group VI, claims 1-8, 11-12, drawn to methods of inhibiting stenosis or restenosis with fibrinogen (Class 514 , subclass 8)

Group VII, claims 1-8, 11-12, drawn to methods of inhibiting stenosis or restenosis with C3bi (Class 514 , subclass 8)

Group VIII, claims 1-8, 11-12, drawn to methods of inhibiting stenosis or restenosis with factor X (Class 514 , subclass 8)

Group IX, claims 1-5, 8-9, 11-12, drawn to methods of inhibiting stenosis or restenosis with ICAM-2 (Class 514 , subclass 8)

Group X, claims 1-5, 8-9, 11-12, drawn to methods of inhibiting stenosis or restenosis

with ICAM-3 (Class 514 , subclass 8)

Group XI, claims 1-5, 8, 11-12, drawn to methods of inhibiting stenosis or restenosis with uPAR (Class 514 , subclass 8)

Group XII, claims 1-5, 8, 11-12, drawn to methods of inhibiting stenosis or restenosis with C36 (Class 514 , subclass 8)

Group XIII, claims 13-15, 17, drawn to compositions comprising Mac-1-specific antibodies (Class 424, subclass 130.1)

Group XIV, claims 13-14, 17, drawn to compositions comprising LFA-1-specific antibodies (Class 424 , subclass 130.1)

Group XV, claims 13-14, 17, drawn to compositions comprising p150,95-specific antibodies (Class 424 , subclass 130.1)

Group XVI, claims 13-14, 17, drawn to compositions comprising CD11d/CD18-specific antibodies (Class 424 , subclass 130.1)

Group XVII, claims 13-14, 16-17, drawn to compositions comprising ICAM-1 (Class 514 , subclass 8)

Group XVIII, claims 13-14, 16-17, drawn to compositions comprising fibrinogen (Class 514 , subclass 8)

Group XIX, claims 13-14, 16-17, drawn to compositions comprising C3bi (Class 514 , subclass 8)

Group XX, claims 13-17, drawn to compositions comprising factor X (Class 514 ,

subclass 8)

Group XXI, claims 13-14, 17, drawn to compositions comprising ICAM-2 (Class 514 , subclass 8)

Group XXII, claims 13-14, 17, drawn to compositions comprising ICAM-3 (Class 514 , subclass 8)

Group XXIII, claims 13-14, 17, drawn to compositions comprising uPAR (Class 514 , subclass 8)

Group XXIV, claims 13-14, 17, drawn to compositions comprising C36 (Class 514 , subclass 8)